ClinicalEvidence

Recurrent miscarriage

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ABSTRACT

INTRODUCTION: Recurrent miscarriage is the spontaneous loss of three or more consecutive pregnancies with the same biological father in the first trimester, and affects 1% to 2% of women, half of whom have no identifiable cause. Overall, 75% of affected women will have a successful subsequent pregnancy, but this rate falls for older mothers and with increasing number of miscarriages. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of treatments for unexplained recurrent miscarriage? We searched Medline, Embase, The Cochrane Library, and other important databases up to June 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 11 studies. After deduplication and removal of conference abstracts, 150 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 137 studies and the further review of 13 full publications. Of the 13 full articles evaluated, two systematic reviews were updated, and one systematic review and one RCT were added at this update. One non-systematic review, two systematic reviews, and one RCT were added to the Comment sections. We performed a GRADE evaluation for five PICO combinations. CONCLUSIONS: In this systematic overview we categorised the efficacy for five interventions, based on information about the effectiveness and safety of aspirin (low dose), corticosteroids, intravenous immunoglobulin treatment, lifestyle adaptation, and progesterone.

QUESTIONS

INTERVENTIONS

Key points

- Recurrent miscarriage is the spontaneous loss of three or more consecutive pregnancies with the same biological father in the first trimester; it affects 1% to 2% of women, in half of whom there is no identifiable cause.

  Overall, 75% of affected women will have a successful subsequent pregnancy, but this rate falls for older mothers and with increasing number of miscarriages.

  Recurrent miscarriage causes considerable distress and psychological morbidity.

  Antiphospholipid syndrome, with anticardiolipin or lupus anticoagulant antibodies, is present in 15% of women with recurrent first- and second-trimester miscarriage.

- We examined evidence from RCTs and systematic reviews of RCTs in women with three or more unexplained recurrent miscarriages.

  For many of the interventions, we found few high-quality studies available.

  There is a need for further high-quality RCTs in this field to inform clinical practice.

- We don't know whether lifestyle adaptation (to stop smoking, reduce alcohol consumption, and lose weight) or low-dose aspirin increase the likelihood of a successful pregnancy in women with unexplained recurrent miscarriage.

  We found no RCTs on the effects of lifestyle interventions.

  We only found one small RCT (54 women) with low-dose aspirin that met our inclusion criteria. Hence, it was difficult to draw any robust conclusions.

  We found one further larger RCT (364 women) on low-dose aspirin (in women with two or more recurrent miscarriages), which was outside our inclusion criteria for this *BMJ Clinical Evidence* overview.

- We don't know whether progesterone supplementation or corticosteroids reduce miscarriage rates compared with placebo in women with unexplained recurrent miscarriage.

  The evidence on progesterone was difficult to interpret because of methodological weaknesses in the trials, such as quasi-randomisation, and because many of the trials were old.

  However, further RCTs are currently under way, which may clarify the position.

  We found one small pilot RCT on corticosteroids in a sub-group of women with unexplained recurrent miscarriage who had high levels of uterine natural killer (uNK) cells on screening. However, we found no RCTs in the general population of women with unexplained recurrent miscarriage.

- Intravenous immunoglobulin treatment does not seem likely to improve live birth rates compared with placebo in women with unexplained recurrent miscarriage, and it may be associated with adverse effects.

Clinical context

GENERAL BACKGROUND

Recurrent miscarriage is the spontaneous loss of three or more consecutive pregnancies with the same biological father in the first trimester; it affects 1% to 2% of women, in half of whom there is no identifiable cause. It is a cause of considerable distress and psychological morbidity.

FOCUS OF THE REVIEW

Several factors may be involved in the aetiology of recurrent miscarriage. Antiphospholipid syndrome, with anticardiolipin or lupus anticoagulant antibodies, is present in 15% of women with recurrent first- and second-trimester miscarriage. Chromosomal, uterine, and endocrine abnormalities may also cause recurrent miscarriages. This overview focuses on women who do not have an obvious cause for their miscarriages. Their recurrent miscarriages are, therefore, unexplained.

COMMENTS ON EVIDENCE

We found no RCTs on the effects of lifestyle adaptation (smoking cessation, reducing alcohol consumption, and losing weight) and single, small RCTs on the effects of low-dose aspirin and corticosteroids. The latter RCT on corticosteroids was in a sub-group of women with high uterine natural killer (uNK) cells on screening. We found two systematic reviews that pooled data on intravenous immunoglobulins, one of which also produced a sub-group analysis on primary or secondary miscarriages, and whether treatment was before or after pregnancy. The regimens given varied widely between trials. The overall methodological quality on studies examining the effects of progesterone was weak, which made it difficult to draw reliable conclusions. The intervention used, and route of administration, differed in each trial.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, January 2010, to June 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 398 studies. After deduplication and removal of conference abstracts, 150 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 137 studies and the further review of 13 full publications. Of the 13 full articles evaluated, two systematic reviews were updated, and one systematic review and one RCT were added at this update. Two systematic reviews, one non-systematic review, and one RCT were added to the Comment section.

DEFINITION	Recurrent miscarriage is usually defined as three or more consecutive, spontaneous miscarriages occurring in the first trimester, with the same biological father. [1] They may or may not follow a successful birth. About half of recurrent miscarriages are unexplained. [2] It is a cause of considerable distress and psychological morbidity. [3] This overview covers unexplained recurrent miscarriages. We have included RCTs that described their population as women with unexplained recurrent miscarriage, which is usually defined as three or more consecutive, spontaneous miscarriages occurring in the first trimester with the same biological father. Most trials were not explicit about the gestational age at miscarriage, which can be difficult to determine clinically, or whether recurrent miscarriages occurred with the same biological father. Where it was clear that a trial had used a definition that varies from the usual definition of unexplained recurrent miscarriage, we have reported this. We have excluded RCTs undertaken solely in women with antiphospholipid syndrome (APS) from this review.
INCIDENCE/ PREVALENCE	In Western populations, recurrent miscarriage affects 1% to 2% of women of childbearing age, and about half of these are unexplained. [1] [2] Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage. [4]
AETIOLOGY/ RISK FACTORS	Increasing maternal age and number of previous miscarriages increase the risk of further miscarriages. [5]
PROGNOSIS	On average, the live birth rate for women with unexplained recurrent miscarriage is 75% in a subsequent pregnancy, with a miscarriage rate of 20% up to 9 weeks, and a 5% miscarriage rate after this period. [5] However, prognosis varies depending on maternal age and number of previous miscarriages. The chance of a successful subsequent pregnancy after three previous unexplained

miscarriages varies from about 90% in a 20-year-old woman to about 54% in a 45-year-old woman.[5] A 30-year-old woman with two previous unexplained miscarriages has about an 84% chance of a successful subsequent pregnancy; whereas for a woman of the same age with five previous unexplained miscarriages, the success rate drops to about 71%.

AIMS OF INTERVENTION To prevent miscarriage and achieve live birth, with minimal adverse effects of treatment.

OUTCOMES **Live birth rates**; **miscarriage rates**; **adverse effects** in both mother and infant, including perinatal mortality, preterm delivery, or low birth weight.

METHODS **Search strategy** *BMJ Clinical Evidence* search and appraisal June 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to June 2014, Embase 1980 to June 2014, The Cochrane Database of Systematic Reviews 2014, issue 6 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Includion criteria** Study design criteria for inclusion in this review were systematic reviews and RCTs published in English, containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. The minimum length of follow-up required to include RCTs was 1 year or until the end of pregnancy if the woman conceived. We included studies with any level of blinding including those described as 'open', 'open label', or not blinded. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of selected treatments for unexplained recurrent miscarriage?

OPTION INTRAVENOUS IMMUNOGLOBULIN

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 12 .
- Intravenous immunoglobulin treatment does not seem likely to improve live birth rates compared with placebo in women with unexplained recurrent miscarriage and may be associated with adverse effects.

Benefits and harms

Intravenous immunoglobulin versus placebo:

We found two systematic reviews that compared immunoglobulin with placebo in women with unexplained recurrent miscarriage and had slightly different inclusion criteria. [6] [7] The first systematic review (search date 2005) included women with three or more prior miscarriages and/or no more than one prior live birth and/or negative evaluations for non-immunological causes (see Further information on studies). [6] It pooled data on eight RCTs. The second systematic review (search date 2010) included women with three or more consecutive miscarriages before 20 weeks' gestation. [7] It pooled data on six RCTs: five RCTs were included in the earlier review and one RCT was published subsequent to the first review. It excluded two RCTs included in the earlier review. We found one further non-systematic review that reported adverse effects (see Comment). [8]

Live birth rates

Intravenous immunoglobulin compared with placebo Intravenous immunoglobulin treatment seems to be no more effective than placebo at increasing live birth rates in women with unexplained recurrent miscarriage (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[6] Systematic review	Women with unexplained recurrent miscarriage 8 RCTs in this analysis	**Proportion of women having a live birth** 92/159 (58%) with intravenous immunoglobulin 85/144 (59%) with placebo The review reported that the outcome variable of live births after 28 weeks' gestation was expanded to include pregnancies alive after 20 weeks' gestation (relative numbers of each gestation not reported)	OR 0.98 95% CI 0.61 to 1.58 P = 0.94 This analysis was not ITT A sensitivity analysis of RCTs reporting an ITT analysis also found no significant difference between groups (4 RCTs, 279 women, OR 1.18, 95% CI 0.72 to 1.93) See Further information on studies	⟷	Not significant
[7] Systematic review	Women with unexplained recurrent miscarriage 6 RCTs in this analysis	**Live birth rate per participant randomised** 88/139 (63%) with intravenous immunoglobulin 87/133 (65%) with placebo	OR 0.92 95% CI 0.55 to 1.54 P = 0.30 The review also performed a subgroup analysis by type of miscarriage and treatment start time (see Further information on studies)	⟷	Not significant

Miscarriage rates

No data from the following reference on this outcome. [6] [7]

Adverse effects

No data from the following reference on this outcome. [6] [7]

Further information on studies

[6] *Methods* The review also reviewed individual participant data in four RCTs. Two of the RCTs included women with two or more miscarriages, but the review extracted data from them only for women with three or more miscarriages. One RCT included in the meta-analysis was described by the review as comparing paternal white cell immunisation with placebo rather than immunoglobulin. However, this only contributed data for two participants to the meta-analysis.

[7] *Methods* The review reported that all RCTs used block randomisation, and allocation concealment and blinding were achieved in all trials. Two of the included RCTs included women with two or more miscarriages, but the review extracted data from them only for women with three or more miscarriages. It noted that three of the six RCTs specified that the same partner was required. All studies except one were stopped prematurely before reaching the *a priori* planned sample size. It noted that the total IVIG dosage given varied between trials, as did the time of treatment commencement, the period between subsequent doses, duration, and control used (albumin or saline).

[7] *Sub-group analysis* The review found no significant difference between groups when data for primary or secondary miscarriage (defined as recurrent miscarriage after a live birth) were pooled separately (primary: 4 RCTs, 147 women, OR 0.67, 95% CI 0.32 to 1.39; secondary: 3 RCTs, 85 women, OR 1.15, 95% CI 0.47 to 2.84) or when data for treatment before or after pregnancy were pooled (before: 3 RCTs, 121 women, OR 1.21, 95% CI 0.58 to 2.51; after: 3 RCTs, 151 women, OR 0.71, 95% CI 0.34 to 1.47).

Comment:

Adverse effects

One non-systematic review reported that mild adverse events such as fever, headache, nausea, blood pressure changes, and mild tachycardia occur in 1% to 15% of people receiving intravenous immunoglobulin treatment. [8] Rare severe adverse effects include anaphylactic reactions, haemolytic anaemia, viral infection (due to contamination of immunoglobulin), renal failure, and thrombotic events. Most severe adverse reactions tended to occur in people with anti-IgA antibodies. [8]

Since the search date of this *BMJ Clinical Evidence* review, the first review [6] has been updated (to search date 2014), and this will be reported in the next update of this review. However, no further studies were included in the meta-analysis.

OPTION LIFESTYLE ADAPTATION (SMOKING CESSATION, REDUCING ALCOHOL CONSUMPTION, LOSING WEIGHT)

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 12 .
- We found no direct information from RCTs about lifestyle adaptation (smoking cessation, reduced alcohol consumption, losing weight) in women with unexplained recurrent miscarriage.

Benefits and harms

Lifestyle adaptation versus placebo or no treatment:

We found no systematic review or RCTs.

Comment: It is important to look for such studies, as questions to do with lifestyle are commonly asked by women experiencing recurrent miscarriage.

OPTION ASPIRIN (LOW DOSE)

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 12 .
- We don't know whether low-dose aspirin increases the likelihood of a successful pregnancy in women with unexplained recurrent miscarriage.

Benefits and harms

Low-dose aspirin versus placebo:

We found one systematic review (search date 2008), which identified one RCT. [9] We found one subsequent RCT, which was outside our inclusion criteria (see Comment, p 5). [10] We found one systematic review of RCTs of aspirin (search date 2000) in any pregnant women, not specifically those with unexplained recurrent miscarriage, which reported on adverse effects (see Comment). [11]

Live birth rates

Low-dose aspirin compared with placebo We don't know whether low-dose aspirin is more effective than placebo at increasing live birth rates in women with unexplained recurrent miscarriage, as we found insufficient evidence from one small RCT (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[9] Systematic review	54 women with recurrent miscarriage without antiphospholipid syndrome Data from 1 RCT	**Proportion of women who had a live birth** 22/27 (81%) with low-dose aspirin 22/27 (81%) with placebo These data were based on 54 women without antiphospholipid syndrome who were part of a larger RCT (82 women) of women with and without antiphospholipid syndrome	RR 1.00 95% CI 0.78 to 1.29 P = 1.0 The RCT had a small sample size, the method of randomisation was not stated, and allocation concealment was unclear	⟷	Not significant

Miscarriage rates

No data from the following reference on this outcome. [9]

Adverse effects

No data from the following reference on this outcome. [9]

Comment:

Adverse effects

We found one systematic review in pregnant women, but not specifically those with unexplained recurrent miscarriage. [11] It found no significant difference between aspirin and placebo in perinatal mortality or neonatal bleeding (perinatal mortality: 20 RCTs, 28,208 pregnant women, 2.9% with aspirin 20 mg to 150 mg daily *v* 3.1% with placebo, RR 0.92, 95% CI 0.81 to 1.05, absolute numbers not reported; 13 RCTs, with aspirin up to 75 mg daily *v* with placebo, RR 0.92, 95% CI 0.78 to 1.09, absolute numbers not reported; neonatal bleeding: 12 RCTs, 26,058 pregnant women, RR 1.03, 95% CI 0.86 to 1.25, absolute numbers not reported).

We found one subsequent RCT (364 women, age 18–42 years, about 16% with inherited thrombophilia), which compared low-dose aspirin plus nadroparin (123 women), low dose aspirin alone (120 women; 80 mg), and placebo (121 women) in women who were attempting to conceive or were less than 6 weeks pregnant. [10] We have reported data on the low-dose aspirin alone and placebo arms only. In this RCT, recurrent miscarriage was defined as at least two miscarriages at 20 weeks or less, which is below the inclusion criteria of this *BMJ Clinical Evidence* review. It was not specified whether the same partner was involved. Of women included in the aspirin alone and placebo arms of the RCT, 145/241 (60%) had had three miscarriages or more. The RCT did not

report data separately for women with three miscarriages or more. Overall, the RCT found no significant difference between groups in live births (61/120 [51%] with aspirin *v* 69/121 [57%] with placebo, RR 0.89, 95% CI 0.71 to 1.13). It also found no significant difference between aspirin and placebo in miscarriage (absolute risk difference +5.2, 95% CI –6.1 to +16.6), premature delivery (absolute risk difference –2.7, 95% CI –8.4 to +3.1), or in small for gestational age (10th percentile: absolute risk difference +4.3, 95% CI –5.7 to +14.4). [10] The trial was discontinued at a second interim analysis 18 months after study recruitment "because of futility".

Clinical guide
Low-dose aspirin is often used empirically for the treatment of recurrent miscarriage. This practice is not currently supported by the evidence.

OPTION PROGESTERONE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 12 .
- We don't know whether progesterone supplementation reduces miscarriage rates compared with placebo in women with unexplained recurrent miscarriage.
- One meta-analysis found weak evidence of benefit with progesterone. However, these data were based on old, small, weak RCTs (with quasi-randomisation and other methodological flaws) from which it was not possible to draw robust conclusions.
- Evidence is limited and there is a need for further high-quality RCTs.

Benefits and harms

Progesterone versus placebo:

We found one systematic review (search date 2013) comparing progestogens with placebo or no treatment. [12] The review included all women in the first 20 weeks of pregnancy. We have only reported the analysis in women with three or more miscarriages. [12] We also found one retrospective observational study in women who had received infertility treatment, which reported on adverse effects (see Comment). [13]

Miscarriage rates

Progesterone compared with placebo/no treatment Progesterone may be more effective than placebo or no treatment at reducing miscarriage in women with unexplained recurrent miscarriage. However, evidence was very weak and should be interpreted with caution (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[12] Systematic review	Women with a history of 3 or more consecutive miscarriages 4 RCTs in this analysis	**Proportion of women who had a miscarriage** 24/132 (18%) with progesterone 35/93 (38%) with placebo or no treatment	OR 0.39 95% CI 0.21 to 0.72 P = 0.0027 These results should be interpreted with caution The included RCTs had weak methods including quasi-randomisation (see Further information on studies) The review also reported an analysis in women with a history of 2 or more recurrent miscarriages (see Further information on studies)	●●○	progesterone

Live birth rates

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	Pregnant women Data from 1 RCT	**Fetal genital tract abnormalities/virilisation** 0/71 (0%) with oral dydrogesterone 0/34 (0%) with no treatment	OR not estimable The RCTs had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Fetal genital tract abnormalities/virilisation** 0/11 (0%) with IM hydroxyprogesterone 0/7 (0%) with placebo	OR not estimable The RCT had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Neonatal death** 2/71 (2.8%) with oral dydrogesterone 1/34 (2.9%) with no treatment	OR 0.96 95% CI 0.08 to 11.00 The RCTs had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Neonatal death** 1/49 (2%) with progesterone pellets 0/40 (0%) with no treatment	OR 6.15 95% CI 0.12 to 316.22 The RCTs had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Preterm birth** 5/71 (7%) with oral dydrogesterone 3/34 (9%) with no treatment	OR 0.78 95% CI 0.17 to 3.61 The RCTs had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Preterm birth** 1/18 (6%) with oral medroxyprogesterone 1/26 (4%) with placebo	OR 1.47 95% CI 0.08 to 25.46 The RCTs had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Preterm birth** 6/11 (55%) with IM hydroxyprogesterone 3/7 (43%) with placebo	OR 1.56 95% CI 0.25 to 9.81 The RCTs had weak methods (see Further information on studies)	⟷	Not significant
[12] Systematic review	Pregnant women Data from 1 RCT	**Preterm birth** 2/49 (4%) with progesterone pellets 1/40 (3%) with no treatment	OR 1.62 95% CI 0.16 to 16.14 The RCTs had weak methods (see Further information on studies)	⟷	Not significant

Further information on studies

[12] *Methods* Although two of the four RCTs included women with two or more miscarriages, the review extracted data from these trials on women with three or more previous miscarriages. The review reported that the trials

included in the meta-analysis had weak methods including quasi-randomisation. Of the four RCTs, the first RCT randomised by the day of the week of attending clinic, blinding was unclear, and the control group had no treatment. The second RCT randomised by sequentially numbered bottles, it was not clear who was responsible for the coding, and control was placebo. The third RCT alternated women between study groups, and it was also unclear who decided which group would be active or placebo. The RCT was reported to be at high risk of attrition bias (30 women analysed of 56 randomised). In the fourth RCT, which was based in two centres, one centre allocated by alternation, while the other centre used randomisation, although the method was not described, blinding was unclear, and the control group had no treatment. Three of the trials reported were old (reported in 2005; 1964; 1953). The included RCTs examined the effects of oral dydrogesterone, oral medroxyprogesterone, IM hydroxyprogesterone, and progesterone pellets inserted into muscle.

Comment:

One retrospective cohort (913 women [1016 pregnancies] who had received infertility treatment) found no significant difference between medroxyprogesterone acetate (4.1%) and control (3.5%) in the incidence of infant congenital abnormalities (reported as not significant, P value and absolute numbers not reported). [13]

We found one further systematic review (search date not reported), which noted that one further study on the effects of oral dydrogesterone (77 women) and one trial of vaginal progesterone pessaries (the PROMISE trial) was under way. [14] [15]

Clinical guide

There is no evidence to support routine use of progestogen to prevent miscarriage in early to mid-pregnancy. There seems to be evidence of benefit in women with a history of recurrent miscarriages, albeit from low-quality, old RCTs. More trials are needed.

OPTION CORTICOSTEROIDS

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 12 .
- We found one small pilot RCT, which examined the effects of prednisolone in the sub-group of women with unexplained recurrent miscarriage and a high level of uterine natural killer (uNK) cells on screening.
- The RCT found insufficient evidence to draw reliable conclusions.
- We found no RCTs in women without a high level of uNK cells.

Benefits and harms

Corticosteroids versus placebo:

We found one pilot RCT (40 women, <40 years of age), which compared prednisolone with placebo in women with a prior history of three or more consecutive miscarriages. [16] Eligible women had an endometrial biopsy, and those with high uterine natural killer cells (uNK; 5% or above cell density) were advised to contact the clinic when pregnant. Of 160 eligible women, 72 women were screen positive, and 40 women returned when pregnant for randomisation.

Miscarriage rates

Corticosteroids compared with placebo/no treatment We don't know whether prednisolone is more effective than placebo at reducing miscarriage in women with unexplained recurrent miscarriage who have high uNK cells on screening (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[16] RCT	40 women with 3 or more consecutive miscarriages and high uNK cells on screening	**Proportion of women who had a miscarriage** 8/20 (40%) with prednisolone 12/20 (60%) with placebo	RR 0.67 95% CI 0.4 to 1.3 P value not reported The RCT may have been too small to demonstrate clinically important differences (see Further information on studies)	⟷	Not significant

Live birth rates

Corticosteroids compared with placebo/no treatment We don't know whether prednisolone is more effective than placebo at increasing live births in women with unexplained recurrent miscarriage who have high uNK cells on screening (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[16] RCT	40 women with 3 or more consecutive miscarriages and high uNK cells on screening	**Proportion of women who had a live birth** 12/20 (60%) with prednisolone 8/20 (40%) with placebo	RR 1.5 95% CI 0.8 to 2.9 P value not reported The RCT may have been too small to demonstrate clinically important differences (see Further information on studies)	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] RCT	40 women with 3 or more consecutive miscarriages and high uNK cells on screening	**Proportion of women who delivered preterm at <37 weeks** 1/20 (5%) with prednisolone 0/20 (0%) with placebo	RR 3.0 95% CI 0.1 to 69.5 P value not reported	⟷	Not significant

Further information on studies

[16] The RCT noted that limitations included lack of power to test efficacy or safety, there was some inconsistency in the start date of trial medication, and that this may have affected the outcome in the active treatment group.

Comment: **Clinical guide**
There is considerable recent interest in the presence of natural killer cells in women with recurrent miscarriage. It is not known whether serum levels or uterine levels are the most important, nor the best way to measure them. It is hoped that further trials will be performed to help elucidate this area of interest in recurrent miscarriage.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Aspirin (low dose) One systematic review [11] and one RCT [10] added to Comment section. Existing evidence re-evaluated. Categorisation unchanged (unknown effectiveness).

Corticosteroids One RCT added. [16] Evidence re-evaluated. Categorisation unchanged (unknown effectiveness).

Intravenous immunoglobulin treatment One systematic review [6] updated and one systematic review [7] added. Existing evidence re-evaluated. Categorisation unchanged (unlikely to be beneficial).

Progesterone One systematic review updated. [12] One systematic review added to Comment section. [14] Categorisation unchanged (unknown effectiveness).

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Disclaimer

GRADE **Evaluation of interventions for Recurrent miscarriage.**

Important outcomes				Live birth rates, Miscarriage rates					
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of selected treatments for unexplained recurrent miscarriage?									
9 (at least 303) [6] [7]	Live birth rates	Intravenous immunoglobulin versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for weak methods (studies stopped prematurely, no ITT analysis, unclear if same partner in some RCTs)
1 (54) [9]	Live birth rates	Low-dose aspirin versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and for weak methods (randomisation not stated, allocation concealment not clear)
4 (223) [12]	Miscarriage rates	Progesterone versus placebo	4	–3	0	0	0	Very low	Quality points deducted for quasi-randomisation, unclear blinding, high risk of attrition bias in 1 RCT, no treatment rather than placebo in 2 RCTs
1 (40) [16]	Miscarriage rates	Corticosteroids versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, restricted population (high uNK), and weak methods (inconsistency in start of trial medication, which may have affected outcomes)
1 (40) [16]	Live birth rates	Corticosteroids versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, restricted population (high uNK), and weak methods (inconsistency in start of trial medication, which may have affected outcomes)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.